Title: Characterisation and Epidemiology of Breakthrough Cancer Pain in Spain

NCT Number: NCT02899884

SAP Approve Date: January 24, 2017

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
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"Characterisation and Epidemiology of Breakthrough Cancer Pain in Spain"

Study CARPE-DIO

CCI [redacted] Project No. TAK125004

Statistical Analysis Plan

Version 2.0
January 24th, 2017

PPD [redacted]

1. HISTORY OF REVISION (Documentation of changes)

SECTIONS	VERSION	DATE REVISED	REVISED BY	DESCRIPTION OF CHANGES
6.2., 6.4 and 8.	1.0	22/01/2017	PPD	Request for additional analyses

INDEX

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis for CARPE-DIO study. In it is described all consideration over study data and are defined the tables, figures and listing (TLFs) that will be presented as result of the study.

Additionally includes definition of the different population and missing data consideration.

The statistical analysis plan will be signed and per protocol dataset will be defined before database lock.

Table of abbreviations

BCP	Breakthrough Cancer Pain
SD	Standard Deviation
Karnofsky PS	Karnofsky Performance Status
95% CI	95% Confidence Interval
BPI	Brief Pain Inventory

3. SYNOPSIS

3.1. Study title

"Characterisation and Epidemiology of Breakthrough Cancer Pain in Spain"

3.2. Study Code

CARPE-DIO Study.

3.3. Sponsor

Takeda Farmacéutica España S.A.
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3.4. Design

This is a cross-sectional, non-PAS, non-interventional, epidemiological study. Given the observational and cross-sectional nature of the study, the protocol does not include any interventions with regard to patient follow-up by the investigator.

This study is a 'non-interventional study' and will follow the guidelines for GPP. This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.

3.5. Objectives

Primary:

- To estimate the prevalence of breakthrough cancer pain in an unselected representative cohort of cancer outpatients with or without pain who attend consultations at Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units at participating sites.

  The estimated annual prevalence will be calculated relative to the population of cancer patients with or without pain seen in participating practices over one month.

Secondary:

- To estimate the annual incidence of patients with breakthrough cancer pain relative to the population of cancer patients with or without pain seen in participating practices over one month.
- To characterize breakthrough pain in patients with cancer pain based on medical history, etiology and pathogenesis, tumour type, location, stage, comorbidities, etc., as well as other clinical characteristics (type of breakthrough pain, number of episodes per day, duration and intensity, and baseline pain management). This information will be collected with the tools used for the clinical assessment of breakthrough pain.
- To assess the prevalence of each of the different causes of pain.
- To determine the percentage of patients who present each of the different profiles/types of breakthrough cancer pain (characterization/classification) and classify them based on the results obtained in the Alberta and BPI questionnaires.
- To determine the percentage of patients who present each of the profiles/types of breakthrough cancer pain and assess possible relationships with demographic characteristics and other clinically significant variables related to the cancer such as diagnosis, pain intensity, comorbidities, etc.
- To assess the quality of life of patients with breakthrough cancer pain and its possible relationship with demographic characteristics and other clinically significant variables related to the cancer or to the breakthrough pain such as etiology, frequency of episodes, pain intensity, time until peak of pain, crisis duration, cause, etc.
- To assess the performance status of patients using the Karnofsky scale in order to know the degree of general wellbeing and ability to cope with activities of daily living presented by the patients studied.

3.6. Total number of subjects

It is estimated that more than 10 patients per day attend consultations for cancer in Medical Oncology, Radiotherapeutic Oncology, Hematology and Palliative Care Departments and around 5 patients in Pain Units. Breakthrough cancer Pain (BCP) is a common and incapacitating subtype of pain that affects a percentage of patients with cancer that varies between 40% and 90% according to different publications. Conservatively, it is expected to detect the prevalence in 50% of patients, and it is estimated that at each site a total of approximately 200 patients, or around 13,200 across the 66

planned sites, will be interviewed on the prevalence of breakthrough cancer pain. This sample will enable us to detect the prevalence of breakthrough pain with a 95% confidence interval and precision of ±1%.

For the assessment of the secondary objective, i.e., characterizing the breakthrough pain based on etiology, underlying pathology and other clinical characteristics, if it is considered the detection of common characteristics in at least 10% of patients in our population to be representative, it will be necessary to recruit 529 patients in order to detect said characteristics with a 95% confidence interval and precision of ± 2.5%.

3.7. Inclusion Criteria

- Patient ≥ 18 years old.
- Patients with baseline cancer pain that is adequately controlled with opioids.
- Presence of episodes of breakthrough pain associated with the cancer pain.
- Meeting the diagnostic criteria for breakthrough cancer pain (patient history and Portenoy's criteria) and the Davies algorithm.
- Patients who are not receiving treatment for breakthrough pain. It is not permitted the inclusion of patients receiving treatment for breakthrough cancer pain in order to avoid bias that may involve the treatment for the characterisation of breakthrough pain.
- Signing of the informed consent.

3.8. Exclusion Criteria

- No severe mental illness.
- Any medical condition or situation complicating the collection of study data as determined by the investigator is not permitted.

3.9. Study treatment

The patients participating in this cross-sectional, non-PAS, non-interventional study will not receive treatment in relation to the study aside from the treatment already prescribed by their usual physician.

4. STUDY POPULATIONS

4.1. Definition of study populations to analyze

Prevalence Study Population: To estimate the prevalence of breakthrough cancer pain will be used all data from patients collected in the prevalence form in the database.

Characterization breakthrough pain Population (Secondary objectives Population): All patients who meet the selection criteria and have given their informed consent will be included in the breakthrough pain characterization and quality of life study.

4.2. Disposition of subjects

A flowchart will be provided to describe the total included patients in each part of analysis:

- To estimate the prevalence of breakthrough cancer pain.
- To characterize breakthrough pain.

Discrepancies between the numbers of patients of each part of analysis will be described by number of patient, site and the reason of the discrepancy.

4.3. Study Discontinuations

Not applicable.

5. PREVALENCE STUDY RESULTS

5.1. General considerations

The prevalence study results will be performed in the "prevalence study population".

As this is an epidemiological study, no imputation on the missing data will be calculated.

Valid percentages will be presented, that is, the real number of observations available in each variable will be used as the denominator. The number of missing data for each variable will be indicated.

5.1. Primary objective analysis

In the prevalence study the following variables will be collected:

- Patient with cancer pain: yes/no
- Breakthrough cancer pain: yes/no
- Diagnostic of BCP: Previously diagnosed; Diagnosed during the visit (according Davies algorithm)
- Date of visit.
- Age.
- Gender.
- Karnofsky PS (0 to 100).
- Type of tumour: head and neck, colorectal, esophagus, stomach, liver, leukemia, lymphoma, breast, multiple myeloma, bone and muscular, ovarian, pancreas, prostate, lung, kidney, central nervous system, testicle, uterus, bladder and other).
- Stage (I-IV).

The prevalence of breakthrough cancer pain and corresponding 95% confidence interval (95%CI) will be calculated as the percentage of subjects presenting breakthrough pain among patients with cancer pain controlled with opioids, collected by all investigators over one month.

Formula:

Prevalence of breakthrough cancer pain (%) = [Number of patients with breakthrough cancer pain / total number of patients registered with cancer pain] x 100.

The estimated annual prevalence will be calculated relative to the population of cancer patients with or without pain seen over one month.

5.2. Secondary objective analysis

To describe the population the following variables will be analyzed:

- Patient with cancer pain: yes/no
- Breakthrough cancer pain: yes/no
- Diagnostic of BCP: Previously diagnosed; Diagnosed during the visit (according Davies algorithm)
- Date of visit.
- Age.
- Gender.
- Karnofsky PS (0 to 100).
- Type of tumour: head and neck, colorectal, esophagus, stomach, liver, leukemia, lymphoma, breast, multiple myeloma, bone and muscular, ovarian, pancreas, prostate, lung, kidney, central nervous system, testicle, uterus, bladder and other).
- Stage (I-IV).

In the prevalence study we will calculate the following results:

- The prevalence of breakthrough cancer pain (primary objective) according to gender (separately for men and women) and corresponding 95%CI.
- The prevalence of breakthrough cancer pain (primary objective) according to age (separately for the following categories: < 70years; ≥ 70years) and corresponding 95%CI.
- The prevalence of breakthrough cancer pain (primary objective) according to specialty (separately for the following categories: Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units) and corresponding 95%CI.
- The prevalence of breakthrough cancer pain (primary objective) according to Karnofsky PS (separately for all categories of PS) and corresponding 95%CI.
- The prevalence of breakthrough cancer pain (primary objective) according to type of tumour (separately for all categories of type of tumour) and corresponding 95%CI.
- The prevalence of breakthrough cancer pain (primary objective) according to Stage (separately for I, II, III and IV) and corresponding 95%CI.
- The prevalence of new cases of breakthrough cancer pain and corresponding 95%CI.

  Formula:

  Prevalence of new cases of breakthrough cancer pain (%) = [Number of patients with breakthrough cancer pain that were diagnosed during the visit / total number of patients registered with cancer pain] x 100.
- The prevalence of breakthrough cancer pain over the total of patients with cancer and corresponding 95%CI.

  Formula:

  Prevalence of breakthrough cancer pain (%) = [Number of patients with breakthrough cancer pain / total number of patients registered with cancer] x 100.

6. CHARACTERIZATION BREAKTHROUGH PAIN ANALYSIS

6.1. Demographic and baseline description. General considerations

The demographic and baseline description will be performed for all "analyzed patients".

Given the descriptive nature of the study, the statistical methodology used will be based primarily on an exploratory analysis of the data through the calculation of descriptive parameters.

The continuous variables will be summarized in a table showing the mean, median, standard deviation and maximum-minimum range and the categorical variables will be presented as absolute frequencies and percentages.

6.2. Subject Characteristics

The analysis of continuous variables will be described by the mean, median, standard deviation, minimum and maximum. This analysis included the age of patients.

The analysis of categorical variables will be described by the distribution of frequencies and percentages. This analysis included the following variables:

- Gender.
- Race.
- Age (< 70 years and ≥ 70 years).

6.3. Diagnosis of cancer

The analysis of continuous variables included the following variables:

- Time from first diagnostic of cancer (time in months from the date of fist diagnostic of cancer until the date of informed consent).
- Time from current treatment of cancer (separately for surgery, chemotherapy, radiotherapy and other) defined as the time in months from the date of current treatment until the date of informed consent.

The analysis of categorical variables included the following variables:

- Type of cancer.
- Stage at diagnosis.
- Previous treatments:
    - Previous surgery (yes/no).
    - Aim at prescribing surgery: curative intent or palliative intent.
    - Previous chemotherapy (yes/no).
    - Aim at prescribing chemotherapy: curative intent or palliative intent.
    - Previous radiotherapy (yes/no).
    - Aim at prescribing radiotherapy: curative intent or palliative intent.
    - Other previous treatment (yes/no).
    - Specify other previous treatment.
    - Aim at prescribing other previous treatment: curative intent or palliative intent.
- Current stage.

- Current treatments:
  - Surgery (yes/no).
  - Aim at prescribing surgery: curative intent or palliative intent.
  - Chemotherapy (yes/no).
  - Aim at prescribing chemotherapy: curative intent or palliative intent.
  - Radiotherapy (yes/no).
  - Aim at prescribing radiotherapy: curative intent or palliative intent.
  - Other treatment (yes/no).
  - Specify other treatment.
  - Aim at prescribing other treatment: curative intent or palliative intent.
- Signs and symptoms:
  - Current sign and symptoms (yes/no).
  - If yes,
    - Mucositis (yes/no).
    - Fracture (yes/no).
    - Nausea/vomiting (yes/no).
    - Constipation (yes/no).
    - Peripheral neuropathy (yes/no).
    - Other (yes/no) and specify.
- Comorbidities:
  - Ischemic cardiopathy (yes/no).
  - Ischemic cardiac pathology (yes/no).
  - Peripheral artery disease (yes/no).
  - Cerebrovascular disease (yes/no).
  - Dementia (yes/no).
  - Parkinson's disease (yes/no).
  - Chronic pulmonary disease (yes/no).
  - Connective Tissue Disorders (yes/no).
  - Gastroduodenal ulcer (yes/no).
  - Diabetes (yes/no).
  - Hemiplegia (yes/no).
  - Chronic kidney disease (moderate/severe) (yes/no).
  - Diabetes with target organ damage (yes/no).
  - Chronic hepatopathy (moderate/severe) (yes/no).
  - AIDS (yes/no).
  - Secondary neoplasm / other tumor (yes/no) and specify.
  - Other (yes/no) and specify.

6.4. Breakthrough cancer pain

We will characterize the breakthrough pain based on:

- Etiology (nociceptive, neuropathic or mixed)
- If nociceptive,
    - Somatic nociceptive or visceral nociceptive (question Q2 of Alberta's questionnaire to be completed by physician or nurse).
- Trigger factor of breakthrough pain (spontaneous pain or idiopathic pain / incident pain).
    - If incident pain,
        - Volitional, non-volitional and procedural.
- Location and type of breakthrough pain (BCP type I to IV).
- Pain intensity (Question 3 of BPI scale: Please rate your pain by circling the one number that best describes your pain at its least in the past 24 hours).

6.5. Brief Pain Inventory questionnaire (BPI)

The BPI questionnaire has two sections: pain intensity (4 items) and interference with activities of daily living (7 items). Each item is given a score on a numerical scale from 0 (no pain/interference with activities of daily living) to 10 (worst pain imaginable/maximum impact on activities of daily living).

The results for these 11 items are then used to obtain two overall scores: Pain severity and Pain interference:

- Pain severity: mean of the four pain items.
- Pain interference: mean of the seven interference items.

The data of the BPI scale for the total of patients that complete all the items of the scale will be analyzed. All items of BPI and two overall scores will be described by the mean, median, standard deviation, maximum and minimum.

Appendix 2: BPI User guide

6.6. SF-12 questionnaire

The SF-12 quality of life scale consists of 12 items, from which total scores for the physical and psychological components will be obtained. The correction methods indicated in the scale's validation manual will be used for the total score for each sub-scale, and the mean, median, standard deviation and range will be presented.

Appendix 3. SF-12 questionnaire

6.7. Karnofsky PS

The analysis of Karnofsky PS will be described by the distribution of frequencies and percentages.

6.8. Alberta Breakthrough Pain Assessment Tool

A different Alberta scale will be collected for each type of breakthrough cancer pain (most bothersome breakthrough pain, second most bothersome breakthrough pain and third most bothersome breakthrough pain) presented by the patient, up to a maximum of 3 questionnaires).

Each of the items on the Alberta scale will be described separately by type of breakthrough cancer pain (most bothersome breakthrough pain, second most bothersome breakthrough pain and third most bothersome breakthrough pain), using the mean, median, standard deviation and range to describe the continuous variables and frequency distributions and percentages to describe the categorical variables.

Appendix 4. Alberta Breakthrough Pain Assessment Tool

7. RELATIONSHIP BETWEEN BCP AND DEMOGRAPHIC AND OTHER CLINICALLY SIGNIFICANT VARIABLES

We will provide for the different types of breakthrough pain (BCP type I to IV) the number and percentage or mean (SD) and median (range), as applicable, the following variables:

- Age
- Gender
- Type of cancer
- Current stage (I-III vs IV)
- Previous treatments (yes/no)
- Current treatments
    - Surgery (yes/no)
    - Chemotherapy (yes/no)
    - Radiotherapy (yes/no)
- Comorbidities
- BPI results: Pain severity and Pain interference.
- Etiology (nociceptive, neuropathic or mixed)
- Trigger factor of breakthrough pain (spontaneous pain or idiopathic pain / incident pain).
- If incident pain, then volitional, non-volitional and procedural.
- Questions 4a, 4b, 7 and 8 from Alberta questionnaire.

We will provide the mean, standard deviation, median and range of the physical and psychological components of the SF-12 questionnaire (quality of life of patients with cancer breakthrough pain) according to the following variables:

- Age (<70years; ≥ 70years)
- Gender
- Type of cancer
- Current stage (I-III vs IV)
- Previous treatments (yes/no)

- Current treatments
  - Surgery (yes/no)
  - Chemotherapy (yes/no)
  - Radiotherapy (yes/no)
- Comorbidities
- Etiology (nociceptive, neuropathic or mixed)
- Trigger factor of breakthrough pain (spontaneous pain or idiopathic pain / incident pain).
- If incident pain, then volitional, non-volitional and procedural.
- Location and type of breakthrough pain (BCP type I to IV).
- Questions 4a, 4b, 7 and 8 from Alberta questionnaire.

8. SUBANALYSIS

Given the special characteristics of the elderly population and patients with multiple myeloma, a sub-analysis of pain characterization (points 6.4 to 6.8 of this statistical analysis plan) will be performed in the following samples:

- Patients over 70 years of age.
- Patients with multiple myeloma.

Additionally a sub-analysis of pain characterization (points 6.4 to 6.8 of this statistical analysis plan) will be performed in the following samples:

- Patients included in Medical Oncology Departments.
- Patients included in Hematology Departments.
- Patients included in Radiotherapeutic Oncology Departments.
- Patients included in Pain Units.
- Patients included in Palliative Care Units.

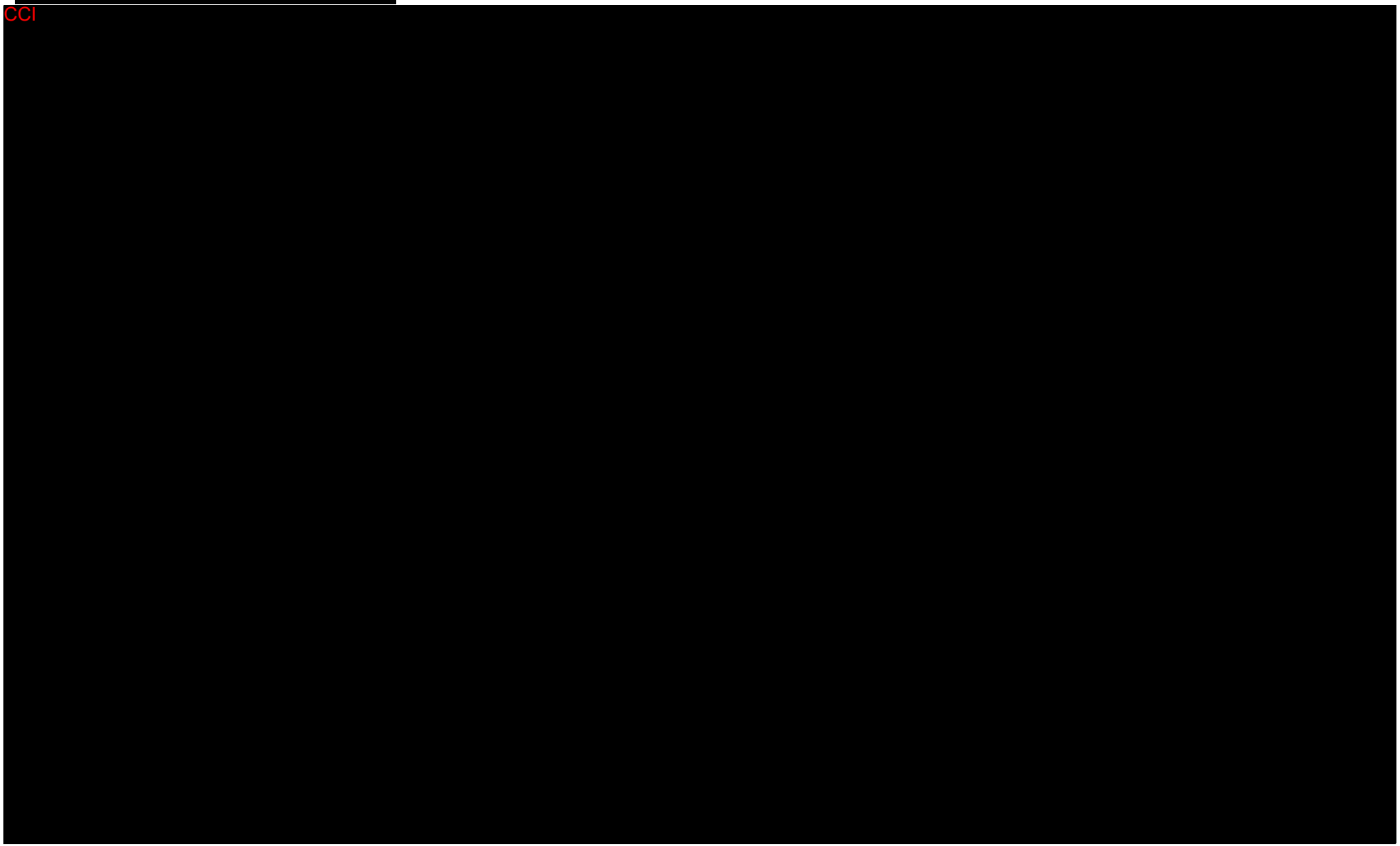
APPENDIX 1: INDEX OF SECTION 14 FOR THE CLINICAL REPORT

The following proposal for section 14 is done according to the pre-defined ICH-format. Minor changes from this planned index do not need to be amended in the SAP.

Comments in Italics will not be printed in table headers or footers.

Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.

CCI [redacted]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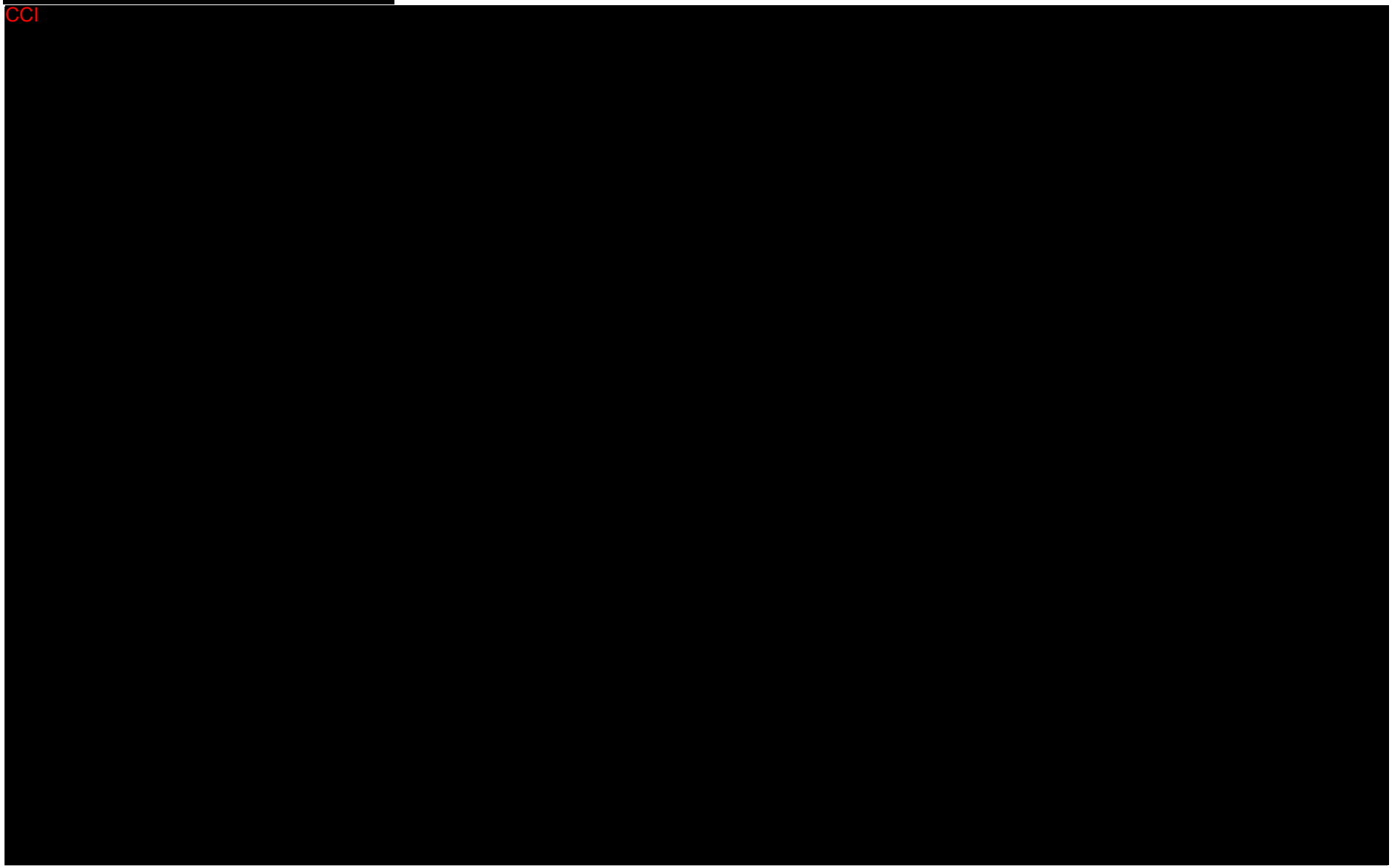
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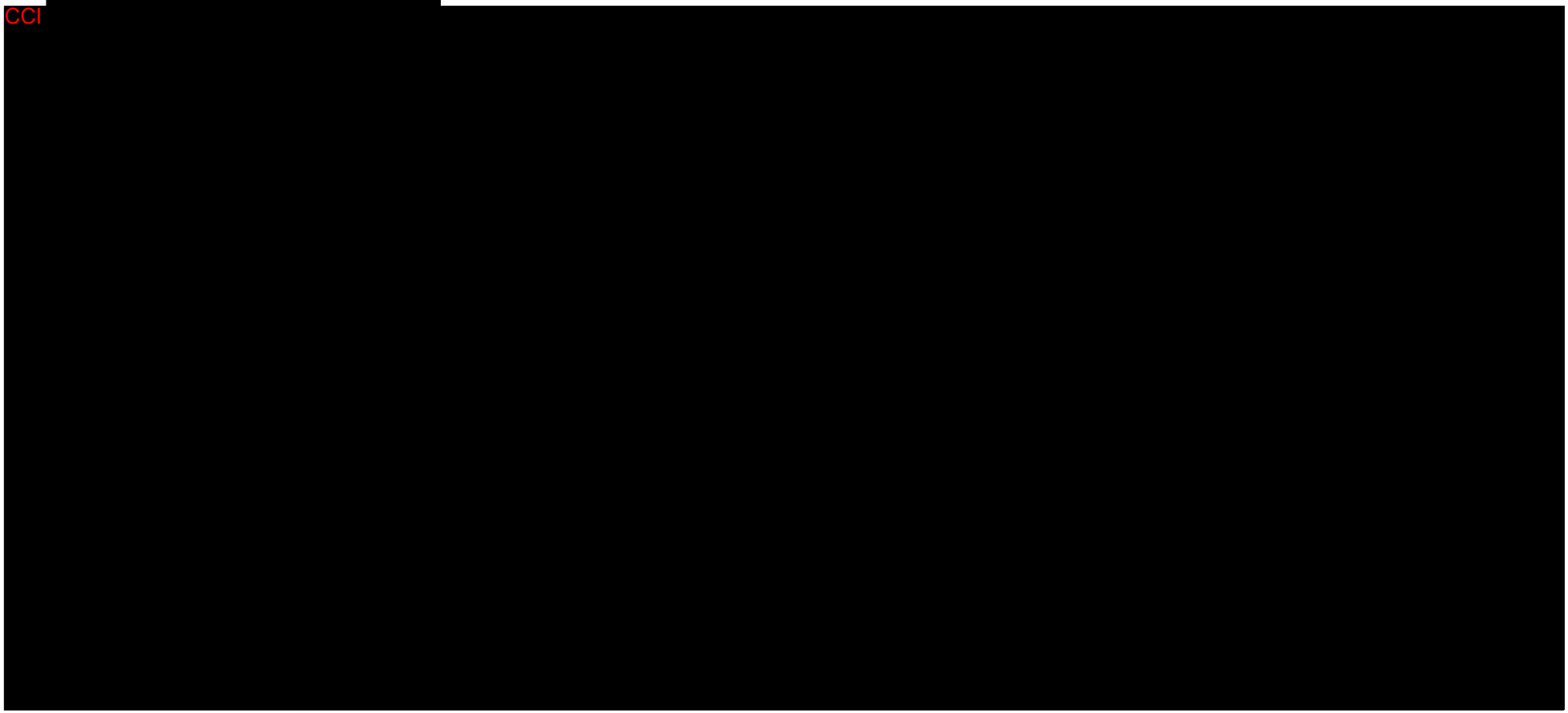

TYPES OF TABLES

Examples for descriptive analysis of categorical variables:

CAT1

		N	%
Variable 1	Value a		
	Value b		
	...		
Variable 2	Value a		
	Value b		
	...		
...			

CAT2

		Variable 2						
		Value a		Value b		...		
		N	%	N	%	N	%	Total
Variable 1	Value a							
	Value b							
	...							
	Total							

CAT3

			95% CI	
	N	%	LL	UP
Variable 1				
Variable 2				
...				

Examples for descriptive analysis of continuous variables:

CONT1

	N	Mean	Median	Standard deviation	Minimum	Maximum
Variable 1						
Variable 2						
...						

CONT2

		Variable 1				
		N	Mean	Median	Standard deviation	Minimum	Maximum
Variable 2	**Value a**						
	Value b						
	...						

APPENDIX 2: BPI USER GUIDELINE

Attached in a separate document

APPENDIX 3: SF-12 QUESTIONNAIRE

The appendix is not attached.

SF-12 scale will be analyzed using the appropriate algorithm provided in the manual of this scale.

APPENDIX 4: ALBERTA BREAKTHROUGH PAIN ASSESSMENT TOOL

Attached in a separate document